Abstract: The Cardiac Energy Grid is a four university collaboration (UW, UM, UCSD, MCW) to develop quantitative thermodynamically-constrained kinetic models describing substrate and energy balance in the functioning heart at rest and during exercise. It is part of the Physiome Project, an international effort to define the physiology, biochemistry and biophysics of organisms using mathematical models. The Physiome approach is cell-centric, considering the cell to be the integrator of signals to drive and organize transcription and proteolysis, and to be a central control element defining structure and function of tissues, organs, and organisms. In this program, multi-scale modeling is central, built upon arrangements of modules defining particular functions. The four teams, working on the different modules and pathways, are bringing their efforts together into a family of multi-scale models.

U01 HL199122 The Cardiac Energy Grid: Modeling Metabolism to Fuel Ion Fluxes and Contraction

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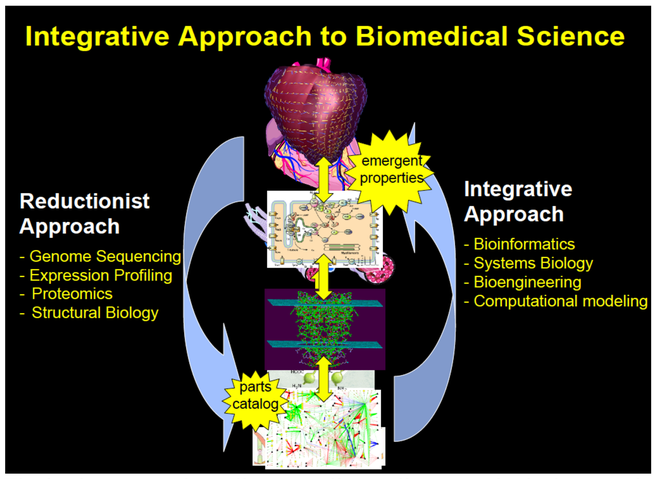
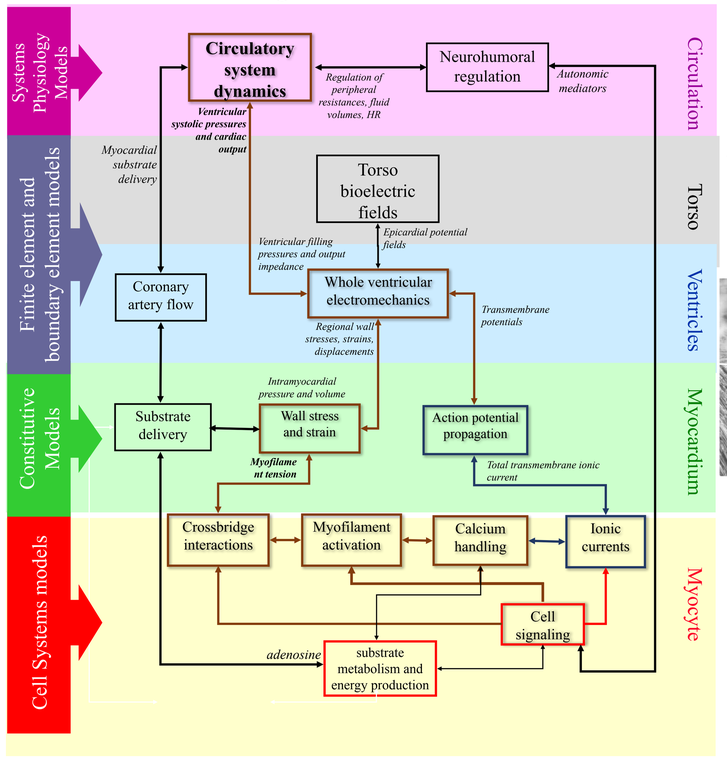
1 Physiome = Quantitative, Integrative Biology



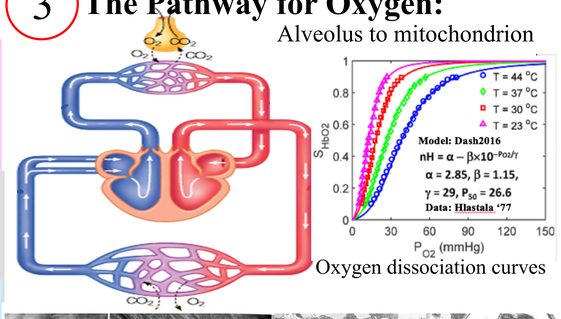
The basic strategy is to dissect reality to discover what's there, and when the pieces are identified, put it back together, organized by pathways, with thermodynamically constrained modules. A goal is to have each module represented at 3 or more levels of complexity: a refined thermodynamically detailed reference module, one or more reduced forms that are accurate in bounded circumstances, and a lowest level that is computationally cheaper yet kinetically correct for particular conditions such as fixed pH. Automated modular reconstruction of models serving a variety of purposes (teaching, research analysis) gives finger-tip selectivity.

2 Modular Structures – Multi-scale integration from molecule to heart

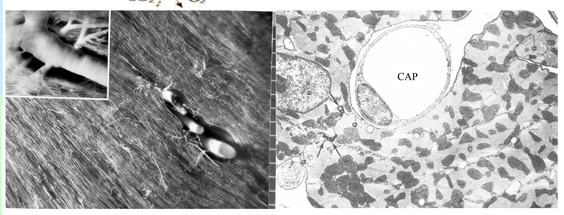


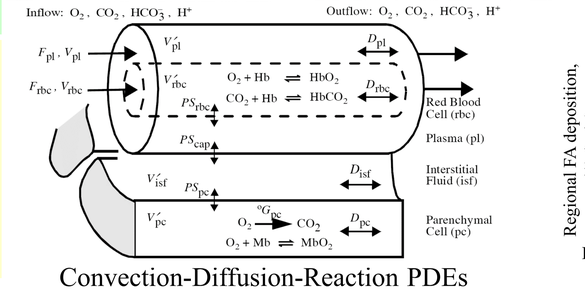
3 The Pathway for Oxygen:

Alveolus to mitochondrion



Oxygen dissociation curves

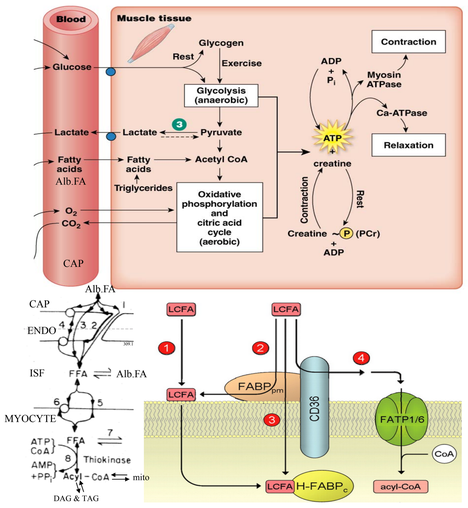


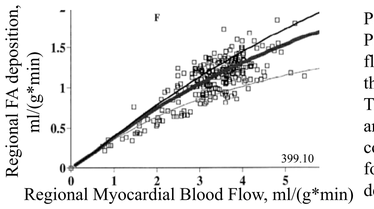


Convection-Diffusion-Reaction PDEs

4 The Pathway for Fatty Acid

Plasma to mitochondrion

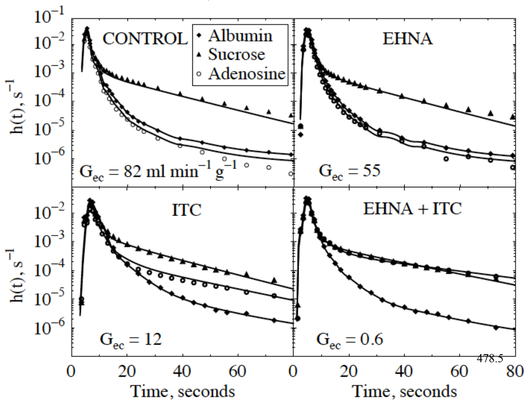


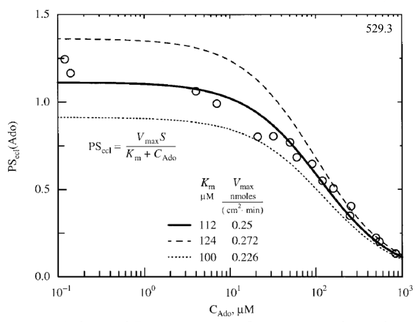


Palmitate permeation, PS_C, is in proportion to flow, F_i. Presumably the transcription of Transporter and the F_i are driven by local ATP consumption required for mechanical force development.

5 Pathway for Nucleosides

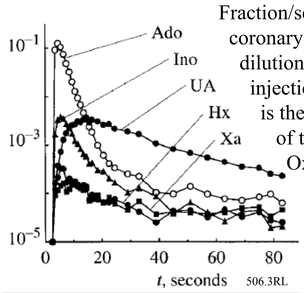
An example in adenosine and inosine transport is blocking by dipyridamole or NBTI. Ado uptake is also blocked if the intracellular metabolism is blocked, deaminase by EHNA, kinase by ITC:





Ado and Ino compete for permeation via a saturable, low affinity, high capacity transporter. The hydrolysis of ATP released with hypoxia -> Ado, causing vasodilation of coronaries, a robust response.

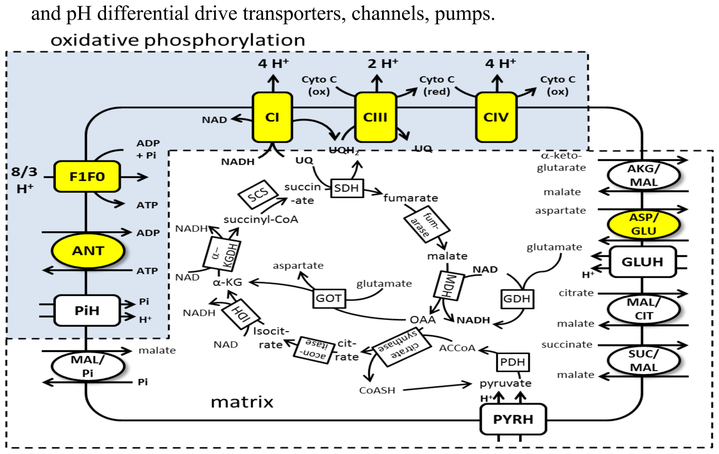
But normally Ado is rapidly degraded to uric acid:



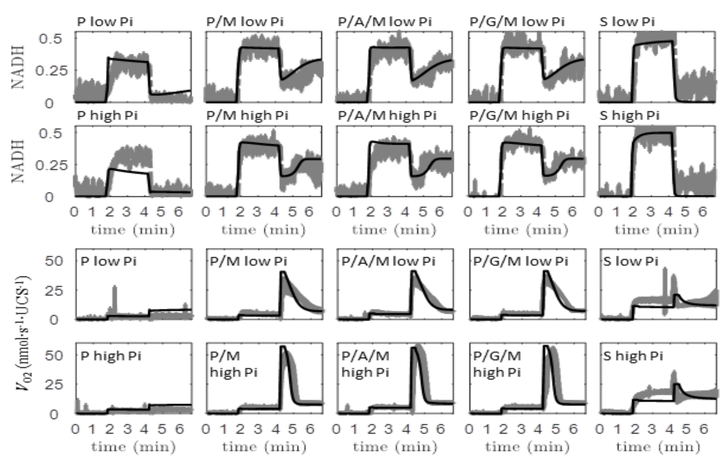
Fraction/second in coronary outflow dilution after bolus injection. Uric Acid is the major product of the Xanthine Oxidase reaction Hx-> Xa ->UA

6 The metabolic energy pathways:

The mitochondrial furnace: Fatty acids, glucose, amino acids and a huge variety of related solutes end up being used for energy production, mostly after preparation for processing in the TCA cycle. Building in the thermodynamics is critical to understanding the energy transfer through the many steps. (Bond graph coding us one way to keep track.) The energy is put into ATP, NADH, FADH. PCr buffers cytosolic ATP/ADP. The mitochondrial membrane potential and pH differential drive transporters, channels, pumps.



tricarboxylic acid cycle and substrate transport

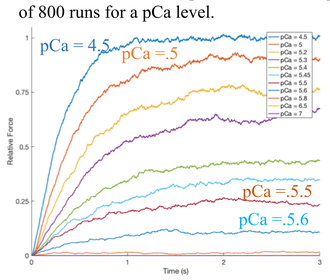


Experiments at UM: At t = 0 min. the oxidized isolated mitochondria are put into buffer. At t = 2 min substrate is added. NADH fluorescence (upper 2 rows) and O_2 consumption (lower) measured. Both signals are sensitive to [substrate]. Model parameters for enzymes and transporters tuned TCA cycle kinetics. **Substrates** were: P: pyruvate, M: malate, A: a-ketoglut, G: glutamate, S: succinate, C: citrate.
Interpretation: TCA cycle has several velocities at once, in different parts, depending on nature and levels of substrates, P_i, and $[O_2]$, etc.

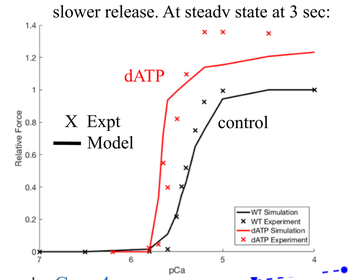
7 Mechanical force development:

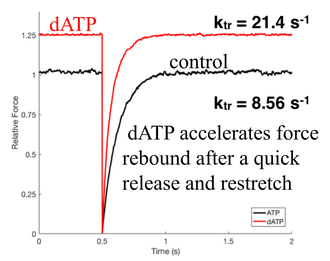
DeoxyATP enhances cardiac contraction: A little dATP does lot to increase force, *in vitro* and *in vivo*. Monte Carlo modeling shows cooperativity in thin filament activation and in cross-bridge cycling through nearest neighbor Tropomyosin and an X-bridge affect on thick filament Myosin. Molecular dynamic simulation shows the Ca / [dATP] relations.

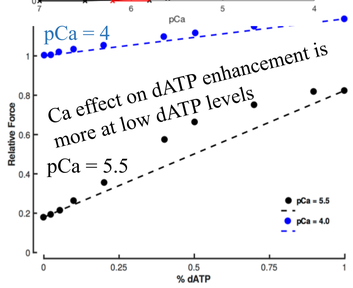
Molecular dynamic calculation of force over 3 sec simulation of Ca step: Each is an average of 800 runs for a pCa level.

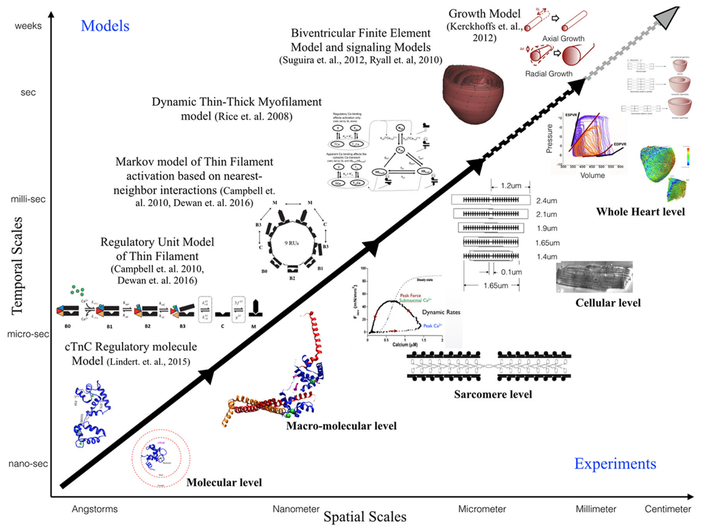


Increase in Force-pCa by dATP occurs by increased rate of myosin binding + slower release. At steady state at 3 sec:









8 Strategies and Tools:

Modular programming: Preconstructed modules for elements, channels, porters, enzymes, each constrained to fulfill mass balance and thermodynamics are linked manually or in automated fashion using MPC or BISEN

JSim, the UW Java-based simulation system, uses a declarative language, MML, for writing the equations directly in near-normal mathematical form, with units, and automated unit balance checking. It is open source at [www.physiome.org/JSim].

BIochemical Simulation Environment, BISEN, from UM, uses modules to creating Matlab for execution.

Continuity, the UCSD finite element package is used for whole heart models for regional spread of excitation and mechanical force development. It uses refined meshes based on experimental measures of cardiac fiber directions.

MPC: Mathematical Program Constructor: Rapid substitution and reformulation of multimodular models of the middle level systems using MPC or BISEN allow us to test the validity of model simplification and the effects on UQ, uncertainty quantification, the ostensible accuracy of prediction. MPC produces JSim code from JSim modules.

Reproducible Model Package is simply a fully used JSim Project File: It can replicate the whole of a model analysis. The package, preserved in ascii, stores code, data sets, notes, runs one or several models (8 ODE, 3 PDE solvers), flexible graphing. It has optimizers (8) for parameter adjustment for model fitting to data, sensitivity analysis, Monte-Carlo analysis, parameter confidence estimates and UQ evaluation. Numerical and optimization methods are kept for each data set.

Model Repository: is The Physiome Model Resource at UW preserves over 400 models in JSim and Matlab. The research models are supported by tutorial models illustrating the principles and building toward the advanced models

Group Communication is fostered through scheduled weekly meetings using Vidyo, a video platform for discussions, presentations, document perusal, critiquing and editing with control at any of the sites or from laptop. It is available anytime for non-scheduled usage as well. **DropBox** also.

U01 Summary: This U01 produces models that are used around the world for research, clinical practice and teaching. It is benefitted by related programs in the four institutions, and in turn provides high quality modeling and quantitative thinking to them and to the field of integrated cardiac function.